Corpus callosum and epilepsies

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SUMMARY
Introduction. Corpus callosum (CC) is the largest forebrain commissure. Structural anomalies and accompanying clinical symptoms are not in the focus of neurologists, epileptologists or neurosurgeons.

Aim and method. Anatomy, embryological development, normal functions, structural abnormalities, additional malformations, clinical symptoms and seizure disorders with CC anomalies are reviewed from the literature sampled during the last ten years and completed by an extensive search within “Elektronische Zeitenschriftenbibliothek” of the Medical University of Innsbruck.

Review. The detection of callosal anomalies increased rapidly with widespread use of brain imaging methods. Agenesis or dysgenesis of corpus callosum (AgCC) might be considered an accidental finding. Epileptic seizures occur in up to 89% of patients with AgCC. The causal relationship correctly is questioned. However, additional causative malformations of midline and/or telencephalic structures can be demonstrated in most seizure patients. The interruption of bilateral spread of seizure activities acts as the concept for callosotomy as epilepsy surgery. Indications are drug-resistant generalized, diffuse, or multifocal epilepsies. A resectable seizure onset zone should be excluded. Most treated patients are diagnosed as Lennox-Gastaut or Lennox-like syndrome.

Conclusions. In cases with callosal abnormalities and clinical symptoms additional malformations are frequently observed, especially with seizure disorders. Callosotomy is the most effective option against drop attacks. The method probably is underused. After callosotomy a circumscribed seizure focus might be unveiled and a second step of resective epilepsy surgery can be successful.

Key words: corpus callosum • agenesis of corpus callosum • additional malformations • seizure disorders • callosotomy • disconnection syndrome

INTRODUCTION
Corpus callosum (CC) is the largest forebrain commissure. Structural anomalies and accompanying clinical symptoms are not in the focus of neurologists, epileptologists or neurosurgeons.

AIM AND METHOD
Anatomy, embryological development, normal functions, structural abnormalities, additional malformations, clinical symptoms and seizure disorders with CC anomalies are reviewed from the literature sampled during the last ten years and completed by an extensive search within “Elektronische Zeitenschriftenbibliothek” of the Medical University of Innsbruck.

REVIEW
Anatomy of corpus callosum
Corpus callosum is by far the largest forebrain commissure with a cross sectional area of between 500 to 600 mm². About 190 million axons cross the midline...
Gross anatomy exhibits a considerable variability with the overall size related to forebrain volume (Jäncke et al., 1997). Furthermore, morphology varies with handedness (Josse et al., 2008) and with age (Suganthy et al., 2003; Garel et al., 2011; Griebe et al., 2011). Conflicting results relate to gender differences (Bishop and Wahlsten, 1997).

Embryology and post-partum development
Rakic and Yakovlev (1968) were the first to study the embryological development of cerebral commissures. At 6-to 8-weeks postconceptional age tissue bridging the midline thickens and develops into two distinct areas. The more ventral part will become the septal area and anterior commissure, the dorsal part forms the fornix, hippocampal commissure, CC and septum pellucidum. Different cellular and molecular mechanisms regulate development (Richards et al., 2004; Paul, 2011). Axons are guided by glial cells (Silver, 1993; Shu and Richards, 2001). Pioneering cingulate axons play a crucial role (Rash and Richards, 2001).

Up to three years after birth the size of CC increases rapidly followed by a slower growth until the middle 20s (Garel et al., 2011). In general, CC shrinks with the aging process. The borders between age-related asymptomatic CC thinning and functional decline are fluent.

Normal functions
Bilateral manual and finger movements are governed by interhemispheric transfer (de Guise et al., 1999; Eliassen et al., 2000; Stancák et al., 2003) and adapted to bilateral sensory (Caillé et al., 2005) as well as auditory modalities (Lessard et al., 2002; Quigley et al., 2003). CC plays a role in the integration of binocular visual information (Aglioti et al., 1993). Hemispheric specialization of language and handedness depend on transcallosal interplay (Witelson, 1985; Funnell et al., 2000; Sammler et al., 2010). Emotion, behavior (Paul et al., 2007), cognition, learning (Suganthy et al., 2003; Peltier et al., 2012), perception of causality and integrated sense of self (Gazzaniga, 2005) are influenced by transcallosal coordination.

Developmental structural abnormalities
Developmental anomalies are classified as dysgenetic, dysplastic and atrophic alterations. Totally absent commissural structures result in complete agenesis, whereas in partial agenesis the commissural plate is short but essentially complete (Paul et al., 2007; Raybaud, 2010).

Complete AgCC (agenesis of corpus callosum) is divided into type 1 and 2 (Schell-Apacik et al., 2008). With type 1, axons are formed but unable to cross the midline. They migrate along the medial hemispheric wall and form aberrant fibre bundles known as Probst bundle. With type 2, no axons are built and no Probst bundles are seen.

Figure 1. Severe intractable epilepsy with mixed seizure types. MRI shows AgCC, periventricular heterotopia, hypoplastic cerebellar vermis, enlarged IV ventricle, atrophic pons. Example of AgCC with additional midline and telencephalic malformations.

Associated malformations with AgCC
Additional malformations of midline and/or telencephalic nervous structures as well as changes of other organs are numerous (Figure 1). Tables 1–3 show an overview. AgCC without substantial involvement of other areas is rarely reported. These cases exhibit subtle or no clinical symptoms and do not come into medical attention. Therefore, the low incidence might be due to a selection bias (Hetts et al., 2006).

Kuchukhidze et al. (2013) as well as Doherty et al. (2013) analyzed midbrain-hindbrain malformations in patients with malformations of cortical development and epilepsy. Twenty six% of patients with additional midbrain-hindbrain malformations exhibited callosal dysgenesis.
Table 1. Malformations of midline structures additional to CC anomalies

<table>
<thead>
<tr>
<th>Malformation</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Holoprosencephaly</td>
<td>Barkovich and Norman, 1988; Barkovich, 1990; Schell-Apacik et al., 2008; Raybaud, 2010</td>
</tr>
<tr>
<td>Chiari - Malformation</td>
<td>Osborn, 1982; Barkovich and Norman, 1988; Glass et al., 2008; Schell-Apacik et al., 2008; Larsen and Raybaud, 2010;</td>
</tr>
<tr>
<td>Dandy-Walker Syndrome</td>
<td>Larsen and Osborn, 1982; Barkovich and Norman, 1988; Schell-Apacik et al., 2008</td>
</tr>
<tr>
<td>Interhemispheric cysts</td>
<td>Larsen and Osborn, 1982; Mori, 1992; Barkovich et al., 2001; Raybaud, 2010</td>
</tr>
<tr>
<td>Cerebellar dysgenesis</td>
<td>Hett et al., 2006; Glass et al., 2008; O’Driscoll et al., 2010; Pisano et al., 2012</td>
</tr>
<tr>
<td>Brain stem anomalies</td>
<td>Hett et al., 2006; Glass et al., 2008</td>
</tr>
<tr>
<td>Septum pellucidum malformations</td>
<td>Raybaud, 2010</td>
</tr>
<tr>
<td>Noncallosal midline anomalies (unspecified)</td>
<td>Hett et al., 2006</td>
</tr>
</tbody>
</table>

Table 2. Telencephalic malformations additional to CC anomalies

<table>
<thead>
<tr>
<th>Malformation</th>
<th>References</th>
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<tbody>
<tr>
<td>Lissencephaly</td>
<td>Barkovich and Norman, 1988; Dobyns et al., 1999; Bonneau et al., 2002; Hett et al., 2006; Schell-Apacik et al., 2008; Kara et al., 2010; Raybaud, 2010; Bravo et al., 2012</td>
</tr>
<tr>
<td>Pachygyria</td>
<td>Barkovich and Norman, 1988; Sztriha et al., 1998; Hett et al., 2006; Schell-Apacik et al., 2008</td>
</tr>
<tr>
<td>Gray matter heterotopia</td>
<td>Barkovich and Norman, 1988; Hett et al., 2006; Schell-Apacik et al., 2008; Pisano et al., 2012; Gonzalez et al., 2013</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>Barkovich and Norman, 1988; Hett et al., 2006</td>
</tr>
<tr>
<td>Polymicrogyria</td>
<td>Hett et al., 2006; Schell-Apacik et al., 2008; O’Driscoll et al., 2010; Raybaud, 2010; Costa Nunes et al., 2013</td>
</tr>
<tr>
<td>Focal cortical dysplasia</td>
<td>Raybaud, 2010</td>
</tr>
<tr>
<td>Cortical malformations (unspecified)</td>
<td>Hett et al., 2006; Glass et al., 2008</td>
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Table 3. Malformations of other organs in subjects with CC anomalies

<table>
<thead>
<tr>
<th>Organ</th>
<th>References</th>
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<tbody>
<tr>
<td>Genitalia</td>
<td>Dobyns et al., 1999; Bonneau et al., 2002; Glass et al., 2008</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Glass et al., 2008</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Glass et al., 2008</td>
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<tr>
<td>Gastrointestinal</td>
<td>Glass et al., 2008</td>
</tr>
<tr>
<td>Vascular</td>
<td>Glass et al., 2008</td>
</tr>
<tr>
<td>Scull deformities</td>
<td>Larsen and Osborn, 1982</td>
</tr>
<tr>
<td>Kidney</td>
<td>Gupta and Lilford, 1995</td>
</tr>
<tr>
<td>Eyes</td>
<td>Gupta and Lilford, 1995</td>
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Prevalence of AgCC

A single incidence/prevalence number is difficult to indicate owing to the complexity of conditions with AgCC, different sample composition/size, methods used and to underrepresentation of cases not coming to medical attention. Larsen and Osborn (1982) reported an incidence of 0.1–0.3% in an unselected hospital population. In a comprehensive data base of a single academic pediatric neurology practice, AgCC was identified in 0.35% of patients (Shevell, 2002). Consecutive MRI scans exhibited AgCC in 1.5–1.6% (McLeod et al., 1987; Bodensteiner et al., 1994). In children with developmental abnormalities, AgCC was observed in 2–3% of children (Bedeschi et al., 2006). After exclusion of destructive lesions or other CNS malformations a population-based study found a prevalence of 1.8 per 10 000 live birth for agenesis or hypoplasia of CC (Glass et al., 2008).

Subtle changes in size and shape of CC can be detected by MRI comparing groups of patients and controls. However, the incidence of these subtle CC anomalies is unknown.

Etiological factors for CC anomalies

Exogenous factors (table 4a and 4b)

In 30–45% of cases of AgCC identifiable causes have been reported (Paul et al., 2007). Table 4a and 4b list identifiable etiological factors for callosal abnormalities as well as CC changes secondary to a known basic disease. One of the most frequently reported risk factor for a small CC is that of very preterm birth. Metabolic diseases are caused by a combination of exogenous and inherited factors. Acquired structural CC abnormali-
### Table 4a. Callosal anomalies secondary to known exogenous factors or basic diseases

<table>
<thead>
<tr>
<th>Exogenous factor/ basic disease</th>
<th>Type of CC anomaly</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born very preterm</td>
<td>Reduced size, altered microstructure</td>
<td>Stewart et al., 1999; Nosarti et al., 2004; Andersen et al., 2006; Kontis et al., 2009; Aukland et al., 2011</td>
</tr>
<tr>
<td></td>
<td>AgCC</td>
<td>Glass et al., 2008</td>
</tr>
<tr>
<td>Normal aging</td>
<td>Reduced size</td>
<td>Ryberg et al., 2008; Griebe et al., 2011</td>
</tr>
<tr>
<td>DAT</td>
<td>↓ thickness in different areas of CC, ↓ FA</td>
<td>Hampel et al., 1998; Tomimoto et al., 2004; DiPaola et al., 2010</td>
</tr>
<tr>
<td>Cognitive disorders MCI</td>
<td>↓ size posterior regions CC</td>
<td>Hensel et al., 2002</td>
</tr>
<tr>
<td>FTD, PSP</td>
<td>↓ total callosal/skull area ratio</td>
<td>Yamauchi et al., 2000</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Reduction in fractional anisotropy, reduced size</td>
<td>McLeod et al., 1987; Ewing-Cobbs et al., 2006; Levin et al., 2000</td>
</tr>
<tr>
<td></td>
<td>Diffuse axonal injury</td>
<td>Friese et al., 2000</td>
</tr>
<tr>
<td>Spastic cerebral palsy</td>
<td>Reduced CC/internal scull surface ratio</td>
<td>Kulak et al., 2007</td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>↓ total callosal/skull area ratio, more pronounced in patients with cognitive decline</td>
<td>Yamauchi et al., 1995</td>
</tr>
</tbody>
</table>

FA – Fractional anisotropy, DAT – Dementia Alzheimer type, MCI – Mild cognitive impairment, FTD – Fronto-temporal dementia, PSP – Progressive supranuclear palsy

### Table 4b. Callosal anomalies secondary to known exogenous factors or basic diseases

<table>
<thead>
<tr>
<th>Exogenous/ basic disease</th>
<th>Type of CC anomaly</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Loss of axons, autopic study</td>
<td>Evangelou et al., 2000</td>
</tr>
<tr>
<td></td>
<td>↓ Fractional anisotropy in subregions</td>
<td>Hasan et al., 2005</td>
</tr>
<tr>
<td></td>
<td>MS-plaques in CC</td>
<td>Friese et al., 2000</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Reduced size</td>
<td>DiPaola et al., 2012</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Encephalomalacic changes, lacunar infarction, extensive leukoaraiosis</td>
<td>Yamauchi et al., 1994; Giroud and Dumas, 1995; Friese et al., 2000; Kim et al., 2012</td>
</tr>
<tr>
<td></td>
<td>Cavernous angioma</td>
<td>Katoh et al., 2013</td>
</tr>
<tr>
<td>Metabolic disorders (inherited and/or acquired)</td>
<td>AgCC + other cerebral malformations</td>
<td>Bamforth et al., 1988; Dobyns, 1989; Nissenkorn et al., 2001; Shevell, 2002; Richards et al., 2004</td>
</tr>
<tr>
<td>Fetal alcohol syndrome, alcoholism</td>
<td>Reduced callosal area + displacement, disrupted microstructure</td>
<td>Sowell et al., 2001</td>
</tr>
<tr>
<td>Cocaine and other street drugs exposure in utero</td>
<td>AgCC + other malformations</td>
<td>Dominguez et al., 1991</td>
</tr>
<tr>
<td>Child neglect</td>
<td>Reduced size</td>
<td>Teicher et al., 2004</td>
</tr>
<tr>
<td>Brain tumor, lymphoma, metastasis</td>
<td>Enhanced lesions</td>
<td>Friese et al., 2000</td>
</tr>
</tbody>
</table>

ties include ischemia, other vascular changes (figure 2a), trauma, hydrocephalus, multiple sclerosis (MS), lymphoma, brain tumors and Wallerian degeneration secondary to cortical lesions (Friese et al., 2000).

**Genetics**

To date, no linked genes have been identified in isolated AgCC. However, in combinations with other CNS-malformations a multitude of causative gene loci have been determined. The mode of inheritance can be autosomal dominant, autosomal recessive or X-linked (Richards et al., 2004; Paul et al., 2007; Schell-Apacik et al., 2008; O’Driscoll et al., 2010; Hanna et al. 2011).

Aicardi described a chromosomally inherited disor-
der with AgCC as cardinal symptom in combination with other, frequently lethal malformations (Kroner et al., 2008). Dysgenesis of CC, other brain anomalies, distinctive EEG and seizures form an entity in the 6q terminal deletion syndrome (Elia et al., 2006). Malformations including AgCC might also be caused by de novo mutations (Sherr et al., 2005; Shimojima et al., 2012).

**Clinical symptoms in cases with CC anomalies**

Statistical correlations of subtle CC changes to psychic/neurologic abnormalities have to be separated from symptoms in cases with absent or grossly reduced CC. Tables 5a and 5b summarize clinical symptoms in combination with CC anomalies. Cognitive dysfunctions are listed together.

The impact of CC anomalies per se is difficult to determine except for isolated CC pathologies. The classic disconnection syndrome includes disturbances of the supplementary motor area, alien hand syndrome, dichotic listening suppression, tactile dysnomia, hemispatial neglect, nondominant hand agraphia, alexia without agraphia, dysarthria and tachistoscopic visual suppression (Jea et al., 2008). Interhemispheric disconnection syndromes were observed after anterior callosal haemorrhage (Leiguarda et al., 1989) and after ischaemic lesions (Giroud and Dumas, 1995; Chung et al., 2013). Neurological symptoms after surgical callosotomies in epilepsies are summarized below.

**Seizures and AgCC**

Numbers of patients with seizures are difficult to interpret because of additional brain abnormalities in most cases. Percentages vary between 27.3% and 89% (Taylor and David, 1998; Shevell, 2002; Doherty et al., 2006; Schell-Apecik et al., 2008). Corresponding reports in cases with isolated AgCC cannot be found. Febrile seizures (Moutard et al., 2003), infantile spasms (Khanna et al., 1994; Li et al., 2007; Conti et al., 2011; Shimojima et al., 2012), Lennox-Gastaut syndrome (Pisano et al., 2012) and several types of focal seizures with or without secondary generalization are described (Taylor and David, 1998; Luef et al., 1992; Pisano et al., 2012; Cordelli et al., 2013). Most reports relate to intractable epilepsies in complex syndromes. Seizures types and severity of epilepsy depend on additional CNS abnormalities and not on AgCC per se. In rare cases CC anomaly represents an accidental finding without a clear-cut causal relation to the epilepsy syndrome (figures 2a and 2b).

**Transitional MRI changes in CC in epileptic patients**

Single case reports and series describe small ovoid focal MRI changes in CC of epileptic patients (Kim et al., 1999; Polster et al., 2001; Cohen-Gadol et al., 2002; Feitová et al., 2002; Mirsatari et al., 2003; Prilipko et al., 2005; Gürtler et al., 2005; Gröppel et al., 2009). These lesions are transient and reversible without persistent consequences. Etiological factors like cytotoxic edema due to seizures, intoxications with AEDs, AED with-

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**Table 5a. Clinical symptoms with callosal abnormalities (excluding seizures)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type of CC anomaly</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>↓ size genu and splenium AgCC</td>
<td>Paul, 2011; Doherty et al., 2006 (6.9% exhibit ADHD)</td>
</tr>
<tr>
<td>Autism</td>
<td>↓ size overall and in subdivisions AgCC</td>
<td>Egaas et al., 1995; Saitoh et al., 1995; Piven et al., 1997; Hardan et al., 2000</td>
</tr>
<tr>
<td>Dyslexia</td>
<td>↓ size in different regions AgCC, AgCC + dysgenesis CC</td>
<td>Doherty et al., 2006 (8.5% exhibit dyslexia); Schell-Apecik et al., 2008 (88% exhibit dyslexia)</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>AgCC, dysgenesis CC AgCC + other malformations of midline structures</td>
<td>Schell-Apecik et al., 2008 (84% exhibit feeding difficulties); Ng et al., 2004</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>AgCC</td>
<td>Nielsen et al., 1992</td>
</tr>
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</table>
drawal, and status epilepticus among others have been discussed. Gröppel et al. (2009) investigated a series of 24 out of 1050 patients and found no statistically significant relation to any of these variables.

Similar transient CC anomalies have been observed with non-epileptic conditions like encephalitis/encephalopathy (Tada et al., 2004; Yaguchi et al., 2005; Bulakbasi et al., 2006; Sreedharan et al., 2011), AED intake in depressive patients without epilepsy (Maeda et al., 2003), brain radiation (Pekala et al., 2003) and other multiple conditions (Doherty et al., 2006; Maeda et al., 2006). Therefore, transient MRI changes in CC are unspecific and causally unexplained.

**Callosotomy as a treatment option**

Van Wagenen and Herren (1940) were the first to suggest a role for callosum section in epilepsy surgery. Methods used are anterior, posterior and total commissurotomy whether in a one-step or a two-step procedure (Fuiks et al., 1991; Cendes et al., 1993; Spencer et al., 1993; Rahimi et al., 2007; Rathore et al., 2007; Tanriverdi et al., 2009). In recent times, radiosurgical callosotomy has been performed (Feichtinger et al., 2006; Bodaghabadi et al., 2011; Moreno-Jiménez et al., 2012).

Indications remain somewhat controversial. Medical intractability and exclusion of a seizure onset zone amenable for resective surgery are considered a prerequisite. Early and recent studies concentrate on intractable generalized seizure types especially drop attacks (Oguni et al., 1991; Carmant et al., 1998; Maehara and Shimuzu, 2001; Majkowska-Zwolinska, 2002; Rathore et al., 2007; Iwasaki et al., 2011). With regard to epilepsy syndromes secondarily generalized epilepsies (Rapaport and Lerman, 1988), Lennox-Gastaut syndrome or Lennox-like syndromes (Kwan et al., 2005; Cukiert et al., 2006), West syndrome (Pinard et al., 1999; Rahimini et al., 2007), and intractable idiopathic generalized epilepsies (Jensen et al., 2006; Iimura et al., 2012) are included. Epilepsies due to bihemispheric cortical dysplasias have also been treated (Landy et al., 1993; Pallini et al., 1995; Vossler et al., 1999; Kawai et al., 2004). The common determinants are medical intractability of severe and disabling drop seizures, best summarized under the term Lennox-Gastaut syndrome.

Outcome of callosotomy by seizures uniformly stresses the good to excellent improvement of drop seizures (Rapaport and Lerman, 1988; Oguni et al., 1991; Cendes et al., 1993; Spencer et al., 1993; Sakas and Phil-
Follow-up studies demonstrated a long-lasting reduction of drop seizures (Sunaga et al., 2009; Tanriverdi et al., 2009). To a lesser degree other generalized seizure types and partial seizures are also improved. Callosotomy represents an effective measure against severe drop attacks. Although patients free of drop seizures are reported, the method has to be regarded as a palliative strategy.

Besides seizure-reducing efficacy, several other positive effects have been reported. Improvements in behavior, attention, overall daily and cognitive functions are observed (Cendes et al., 1993; Maehara and Shimuzu, 2001; Cukiert et al., 2006; Rahimi et al., 2007; Rathore et al., 2007; Yonekawa et al., 2011). Correspondingly, quality of life measures improve (Andersen et al., 1996; Carmant et al., 1998), and parents of patients are satisfied by the postoperative outcome (Gilliam et al., 1996; Yang et al., 1996; Sassower et al., 2001; Rathore et al., 2007).

Neurological symptoms after callosotomy mostly are mild and transient, and include parts of the classical disconnection syndrome (Sass et al., 1990; Fuiks et al., 1991; Andersen et al., 1996; Lausberg et al., 2003). In

**Figure 2a.** Female, 32 years, L-sided temporal lobe epilepsy. Segment of EEG-video recording. Sleep record, sharp wave focus over F7, T3.

**Figure 2b.** Female, 32 years, L-sided temporal lobe epilepsy. MRI shows a cavernous angioma within the CC, considered an accidental finding without a causal relationship to temporal lobe epilepsy.
cases of total sections symptoms are more frequent and can persist (Provinciali et al., 1990; Cendes et al., 1993).

Preoperative EEG changes reflect the selection of patients. Generalized epileptiform discharges like spikes and waves, 2/sec sharp and slow waves, runs of rapid spikes (figure 3a), and generalized ictal patterns have been recorded (Spencer et al., 1993; Oguni et al. 1994; Phillips and Sakas, 1996; Hanson et al., 2002; Kwan et al., 2005; Cukiert et al., 2006). After commissurotomy, disruption of generalized discharges or their complete elimination was observed in the majority of patients (Gates et al., 1984; Spencer et al., 1985; Oguni et al., 1994; Kwan et al., 2005; Cukiert et al., 2006). In about half of patients, the postoperative EEG exhibited a delineated spike focus (Iwasaki et al., 2011; Ono et al., 2011) (figures 3a and 3b). No criteria in the preoperative EEG are known to predict outcome (Makari et al., 1989; Hanson et al., 2002). Improvement in postoperative EEG was correlated with better seizure outcome (Rathore et al., 2007; Yonekawa et al., 2011).

**Options after callosotomy**

Callosotomy is considered a palliative measure. Many patients remain uncontrolled even with drop attacks. After callosotomy an epileptogenic focus might be identified and confirmed as seizure onset zone by invasive methods. Consecutive resective epilepsy surgery resulted in good results (Clarke et al., 2007; Lin et al., 2011; Ono et al., 2011).

Another option in severe generalized, diffuse or multifocal epilepsies is vagus nerve stimulation. A comparison with callosotomy demonstrated a significantly better outcome for callosotomy but a higher risk for complications (Nei et al., 2006; Lancman et al., 2013). Thalamic stimulation after anterior callosotomy was moderately successful in two patients (Capecci et al., 2012).

**CONCLUSIONS**

Commissural abnormalities consist of developmental dys- or agenesis, acquired lesions in the CC, shrinkage

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**Figure 3a.** Female, 24 years of age, tc 1.0 F 70. Lennox-Gastaut syndrome of late onset. Sleep EEG before callosotomy. Bilateral run of rapid spikes.
of fibres due to Wallerian degeneration secondary to forebrain lesions and subtle statistical group changes.

Developmental CC anomalies are part of more extended dysplastic lesions of midline and telencephalic structures in the overwhelming number of cases with neurological symptoms. Specialized imaging studies should be performed to demonstrate these causative lesions.

Subtle group changes in the size and structure of CC are seen with a number of conditions (tables 4a, 4b and 5). The clinical significance of these statistical correlations is unknown.

Epileptic seizures are seen in up to 89%. Seizure types and epilepsies include a variety of focal and generalized disorders and are caused by malformations additional to AgCC.

Surgical callosotomy has been used in untreatable severe epilepsy syndromes not amenable for resective surgery. Most patients suffered multiple seizure types with prominent drop seizures, corresponding to Lennox-Gastaut or Lennox-like syndromes. Outcome after callosotomy is best for drop seizures although no entirely seizure free patients can be expected. With the introduction of new antiepileptic drugs and vagal nerve stimulation the use of callosotomy has decreased. Although callosotomy has a higher risk for complications, the effect on seizure frequency seems to be more pronounced and the procedure is probably underused. The role of callosotomy as a method to unveil a masked resectable seizure focus has to be corroborated by a formal study.

CONFLICT OF INTEREST DISCLOSURE
The authors have no conflict of interest to declare.

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